WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/012093

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/012093

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents cited in the search report:

d1: US-B1-6 274 579
d2: JOURNAL OF CHROMATOGRAPHY A, vol. 1006, no. 1-2, 18 July 2003 (2003-07-18), pages 33-44
d3: WO 99/57089
d4: JOURNAL OF CHROMATOGRAPHY A, vol. 908, no. 1-2, 26 January 2001 (2001-01-26), pages 201-214

2- Novelty
The preparation of optically pure (+)-(2S,3S)-2-(3-chlorophenyl),3,5,5-trimethyl-2-morphinol is disclosed in d1. The chromatographic method for separating the two enantiomers described in column 4 of this document differs from the one of the present invention in that it is not carried out in continuous.
D2 to d4 do not disclose any method for preparing the compound of present claim 1.
Hence, the requirements of Art. 33.2 are met.

3- Inventive step
3.1- D1 is regarded as the closest state of the art since it discloses a method for preparing optically pure (+)-(2S,3S)-2-(3-chlorophenyl),3,5,5-trimethyl-2-morphinol.
The experimental parts of the present application clearly show that it is possible to resolve a mixture comprising the (+) and (-) enantiomers of the morphinol derivative of claim 1 by continuous chromatography. The objective technical problem can therefore be seen in a further process for preparing (+)-(2S,3S)-2-(3-chlorophenyl),3,5,5-trimethyl-2-morphinol.

3.2- The solution of this problem represented by the method of present claims 1 to 16 appears obvious. The skilled person faced with the problem of providing an alternative method to the one disclosed in d1, would find in d2 to d3 the indication to use a continuous chromatography. In particular, he will deduce from d2 that the SMB and Varicol technologies, specifically mentioned in present claims are particularly suitable for preparing pharmaceutically pure compounds (cf. abstracts).
D3, which discloses the application of continuous chromatography in the separation of

the sertraline enantiomers, indicates (cf. page 5) that the undesired enantiomer can be racemised and reintroduced in the continuous chromatography (cf. present claim 13).
From d4, the skilled person would learn that the continuous chromatography can be coupled with the crystallisation in order to improve the enantioseparation (cf. present claim 11).
The preferred eluents and chiral stationary phases of the present process appear to be of common use in the field of continuos chromatography (see for instance Table 1 of d3).
Accordingly, it appears that the skilled person faced with the problem of providing a mere alternative to the process of d1, would find in d2 to d4 all the relevant information to arrive to present process.
Accordingly, claims 1 to 16 do not meet the requirements of Art. 33.3 PCT.